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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,573	RAZ ET AL.	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/16/07; 2/12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17 are pending and under consideration.

Claim Objections

Claim 1 is objected to because of the following informalities: The claim is directed to a nucleic acid that exists in nature and not to an isolated nucleic acid or a nucleic acid encoding a gene product. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of treating irritable bowel syndrome (IBS) in an individual, the method comprising administering to the individual an effective amount of a therapeutic nucleic acid to reduce at least one symptom of IBS in the individual.

The specification nebulously discusses treating irritable bowel syndrome (IBS) in an individual suffering from IBS by administering to the individual an effective amount of a therapeutic nucleic acid and further by administering at least a second therapeutic agent [0017] (and throughout the specification). However, the specification fails to provide any guidance

and/or working examples or any data at all for administering any nucleic acid at an effective level for treating IBS. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed method for treating IBS. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

The claims embrace a method for treating IBS in an individual by administering any type of nucleic acid resulting in the production of a therapeutic protein in a bowel tissue. The specification failed to provide specific guidance or working examples correlating to treatment of IBS one of skill in the art could not rely on the state of the gene therapy art to treat IBS by way of the claimed methods. At the time of filing the art of gene therapy was an unpredictable art with respect cell targeting, levels of expression of a therapeutic protein necessary to provide therapy, and mode of administration of the therapeutic gene. Numerous factors complicate the nucleic acid delivery art, which would not have been shown to overcome by routine experimentation. These include, the fate of the DNA itself (volume of distribution, rate of clearance into tissues, etc), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRMA produced, the stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically on the vector being used and the protein being produced. **Gorecki, 2001** (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy in vivo include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract).

Thomas et al, (Nature, 4: 346-358, 2003) notes that more work is needed to develop site-specific integration vectors, and to improve the ability of vectors to home in on and infect specific target cell populations and understanding how to predict the response of individual patients to inflammatory vectors also remains a substantial challenge (p 356, 1st column, 2nd paragraph).

With regard to the administration of a therapeutic nucleic acid comprising a nucleotide sequence of the formula 5'-CG-3' for treatment of IBS for example, the art teaches that for example administration of 5'-CpG-3' oligonucleotides is unpredictable. **Barbara et al,** [Gut, 51(Suppl I):i41–i44, 2002 (IDS)] note that low grade mucosal inflammation in irritable bowel syndrome (IBS) due to an increased number of inflammatory cells in the colonic and ileal mucosa as a result of episodes of infectious enteritis and changes in bacterial microflora may all play a role in promoting and perpetuating this low grade inflammatory process (abstract). Barbara et al note abnormal neuroimmune interactions may contribute to the altered gastrointestinal physiology and hypersensitivity that underlies IBS thus IBS is associated with intestinal inflammation and infections in the pathogenesis of IBS is given (abstract). **Shanahan et al** (Am J Physiol Gastrointest Liver Physiol 288:417-421, 2005) teach in certain murine models of IBD, bacterial CpG DNA mediates the anti-inflammatory effect by signalling through host TLR9 receptors (p G420, 1st column). CpG DNA motifs may have opposing effects in experimental models of intestinal inflammation depending on the timing of its administration. In contrast to the prophyactic effect of CpG DNA before the onset of inflammation, exposure to CpG DNA during acute inflammation has been shown to exacerbate disease in a murine model of IBD (p G420, 1st column). **Watson et al,** (Clinica Chimica Acta, 364: 1 – 11, 2006) while reviewing the status of the CpG oligonucleotides used to induce suppression of the immune hyperactivity of the GI tract note that "For some cell types direct activation by CpG ODN is

controversial, and may require co-factors: for instance, recently it has been demonstrated that human peripheral NK cells express TLR9 mRNA but functionally respond to CpG ODN (B-type) stimulation only when prestimulated with IL-12 or IL-8 (p 3, 2nd column). Watson also notes "characterization of synthetic ODN raises a number of pertinent issues. Since the synthetic PS-ODN and the natural PO-ODN have different stimulatory properties, one must exercise caution in transposing the effects of CpG-B ODN in a model system to a generalized effect of bDNA. Similarly, the degree of bacterial DNA methylation might represent an important contributing factor to how stimulatory the bacterial DNA is in vivo. Interestingly, nucleotide motifs either within or on discrete CpG ODNs that dramatically reduce the immunostimulatory properties of activatory CpG ODNs have been identified, raising the question of how the eukaryotic cell distinguishes different bacrerial DNA sequences. Genomic sequencing and comparison of pathogen versus commensal DNA is required to address this question. Thus, functionally, the effect of CpG DNA is modulated by base sequence, presence of CpG motifs, and, artificially, by modification of the phosphodiester backbone" (p 3-4). Thus, the therapeutic efficacy of 5'-CpG-3' nucleic acid treatment of IBS is unpredictable. Hence, one of skill in the art cannot predict the therapeutic effects of the formula 5'-CpG-3' nucleic acids in IBS since it appears to depend on the route of administration, dose and timing of administration of the CpG DNA motifs and exposure to CpG DNA has been shown to be associated with the onset of inflammation and its association with the host's immune response resulting in a therapeutic effect in vivo is not consclusive as raised by the state of the art at the time of filing. The disclosure has not taught the therapeutic effects of nucleic acids comprising 5'-CpG-3' in IBS disease when they are administered via any route at any dose.

In light of the above, it appears that the state of the art is suggesting that nucleic acid and the formula of 5'-CG-3' IBS therapy might be feasible in the future. The instant specification

does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of route and dose of administration of a therapeutic nucleic acid for effective IBS therapy raised by the state of the art. The quantity of experimentation required to practice the methods as claimed would require the de novo determination of effective target sites, modes of delivery, safe administration of the oligonucleotide and timing of administration of CpG oligodeoxynucleotides to target appropriate cells and/or tissues in a subject, and further whereby treatment effects are provided for the claimed condition therefore, the skilled artisan would conclude that the state of art of nucleic acid or of the formula of 5'-CG-3' therapy is undeveloped and unpredictable at best.

Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for treating IBS by nucleic acid or of the formula of 5'-CG-3' therapy without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the treatment of IBS, particularly with any nucleic acid or of the formula of 5'-CG-3', the lack of direction or guidance provided by the specification for the treatment of IBS, particularly with any nucleic acid or of the formula of 5'-CG-3', the absence of working examples that correlate to the treatment of IBS, the unpredictable state of the art with respect to the treatment of IBS, particularly with any nucleic acid or of the formula of 5'-CG-3', the undeveloped state of the art pertaining to for the treatment of IBS, particularly with any nucleic acid or of the formula of 5'-CG-3', and the breadth of the claims directed to all types of IBS, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims **1, 14-15, 17** are rejected under 35 U.S.C. 102(b) as being anticipated by Vesely et al, (US 5,716,615; Feb 10, 1998).

To the extent the instant claims read on a method requiring any type of nucleic acid that exists in nature the following rejection over the prior art is applicable.

Vesely et al teach a method for prophylaxis or treatment of gastrointestinal disorders comprising oral administration of several different bacteria such as Streptococcus thermophilus, Lactobacilli species and Bifidobacterium species. Vesely et al teach that said composition can be used to treat gastrointestinal disorders such as diarrhea and irritable bowel syndrome (abstract, column 3 line 41-42, and column 13 claims 18, 21). Vesely discloses the compositions of the invention can be made in conventional pharmaceutical forms, such as for example tablets, coated tablets, capsules, packets, solutions, sachets, suspensions, emulsions, suppositories, pellets, syrups, vaginal suppositories, and are prepared in the usual m manner by mixing active ingredients in the mentioned amounts, eventually adding excipients and/or carriers, adjuvants and/or dispersing agents. Water may be used as the diluent (column, lines 20-40) (**claims 1, 14-15, 17).** To the extent the Streptococcus thermophilus, Lactobacilli species and Bifidobacterium species DNA is therapeutic for gastrointestinal disorders the teaching of Vesely et al anticipate the claimed invention.

Thus, the claimed invention is anticipated by Vesely et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 5, 7-8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 9-14 of U.S. Patent No. 6,613,751. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods in both claims overlap in scope of having to treat IBS via a nucleic acid or the formula of 5'-CpG-3' in a subject. For example, claim 2 of the instant invention is directed to a method for to the administration of a therapeutic nucleic acid comprising a nucleotide sequence of the formula 5'-CG-3'. US 6,631,751 also teaches A method for ameliorating gastrointestinal inflammation in a subject comprising: administering to a subject suffering from gastrointestinal inflammation a formulation comprising an immunomodulatory nucleic acid to the subject, the immunomodulatory nucleic acid comprising the sequence 5'-CpG-3', wherein said immunomodulatory nucleic acid is isolated or synthetic, said administering being in an amount effective to ameliorate a symptom of gastrointestinal inflammation in the subject; wherein said administering is by a route selected from oral and subcutaneous, and wherein gastrointestinal

inflammation is ameliorated in the subject. Thus, the claims of '751 differ only with respect to administering to the subject a 5'-CpG-3' for treating gastrointestinal disorders which IBS is one type of gastrointestinal dosorders. However, in view of the teachings of '751 a 5'-CpG-3' is an obvious variant of 5'-CG-3', as taught in the specification of the instant invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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